REMARKS

I. Status of the Claims

Claims 1-10 and 21 were pending at the time the final Office Action dated February 5, 2010, was mailed. No claims are amended, canceled, or newly added. Claims 1-10 and 21 are therefore pending.

II. Claims 1-3, 8, and 10 Are Patentable Over Aoki and Miyamoto

Claims 1-3, 8, and 10 remain rejected under 35 U.S.C. § 103(a) over the combined teachings of Aoki (EP Patent No. 1 308 156) and Miyamoto et al. (U.S. Patent No. 6,462,093) ("Miyamoto"). Each of these references was analyzed using the guidance of *Graham* Factor Analyses in the previous response dated October 5, 2009 ("the October 2009 response"), incorporated herein, and will not be repeated here. Applicants disagree with the rejection for the reasons presented in the October 2009 response and for the reasons set forth below.

A. The Meaning and Significance of "Modulated" and How This Term Is Not Taught or Suggested By the Art

As an initial point, applicants wish to bring the following element of Claim 1 to the Examiner's attention: "wherein the oscillating electromagnetic field is microwave irradiation modulated to increase the temperature of the mixture to a temperature greater than the melting temperature of the drug and maintained at the temperature greater than the melting temperature of the drug for at least 5 minutes" (emphasis added). Because the prior art does not teach or suggest this aspect of the claims, the claims are not rendered obvious by a combination of Aoki and Miyamoto. See M.P.E.P. § 2143.02 ("A rationale to support a conclusion that a claim would have been obvious is that ***all the claimed elements were known in the prior art***..."); see also *Honeywell Intern., Inc. v. U.S.*, 2010 WL 2037233, 6 (Fed. Cir. 2010) (claimed invention found not obvious in view of failure to prove that cited references disclosed each element of claims). To explain this distinction between the claims and the art, applicants provide the following.

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The specification explains that the "microwave treatment cycle" reflected in Claim 1 is "fundamental" to the claimed invention. Specification, page 7. This cycle involves tuning microwave power

> in such a way that the sample (i.e. the drug-carrier mixture being treated) reaches a temperature value (T°) higher than the melting temperature of the drug contained in the mixture. The temperature T° must then be maintained steady for at least 5 minutes. . . . The microwave treatment can be effected by temporarily setting a specific power level (e.g. 500 W), until the sample reaches the target temperature T°; the latter can be freely chosen by the operator, provided that it is higher than the melting temperature of the drug present in the mixture; once temperature T° is reached, the treatment is prolonged, tuning (modulating) the microwave power so as to maintain the temperature of the sample steady at the temperature T°, for at least 5 minutes.

Id. (emphasis added). The specification further explains how the temperature is maintained via modulation:

> In this respect it is important to remark that a melting substance absorbs energy in irregular way, depending on the relative amount of phases (solid, liquid) it goes through during melting. Therefore a steady administration of electromagnetic energy (microwaves power) during the melting process does not produce a parallel steady temperature in the sample; on the contrary, the thus treated sample inevitably shifts in temperature. In order to maintain the sample at a steady temperature, it is necessary to **modulate** the microwave power, thus compensating continuously for the variable degree of energy absorption of the sample, which takes place during the fusion process. Such compensations are obtainable by available means of electronic systems capable to detect any changes in the sample temperature and to modify immediately, in excess or defect, the microwave power so as to maintain the sample temperature steady at the pre-set T° value.

Id. at page 8 (emphasis added). Applicants bring the claim term "modulated" to the Examiner's attention to emphasize that the claimed method employs such modulation of microwave power so that the claimed mixture may be subjected to a temperature greater than the melting temperature of the drug. In this way, a composite is formed that contains the drug, wherein the

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drug is dispersed inside of the organic carrier particles as well as on the external surface of the particles ("the desired drug dispersal") (see, e.g., Example 1).

Neither Aoki nor Miyamoto teach this microwave irradiation modulation. While both references discuss microwave irradiation, there is no discussion or suggestion regarding modulation of the microwave irradiation to achieve a composite having the desired drug dispersal. Instead, microwave irradiation is delivered at constant power in both references. See, e.g., Aoki, Examples 1-6, and Miyamoto, Examples 4-7; see also page 2 of the present Specification ("In both [Aoki and Miyamoto], the microwave power (Watt) is kept constant throughout the entire treatment").

Further, the Examiner contends that one must add an amorphous state-inducing agent of Miyamoto to a formulation of Aoki to achieve a composite having the desired drug dispersal.[1] Applicants submit that nothing about this methodology renders the use of modulated microwave irradiation obvious, particularly when neither Miyamoto nor Aoki discuss a goal of obtaining composites having the desired drug dispersal. While the desired drug dispersal may be achieved by the methods of Aoki, Miyamoto, or a combination thereof (which applicants do not concede), Aoki, Miyamoto, or a combination thereof do not achieve this result by the claimed method, because Aoki and Miyamoto employ microwave irradiation of constant power and the optional use of an amorphous state-inducing agent, whereas the claimed method employs modulation of microwave irradiation.

The consequence of employing microwave irradiation at a constant power is that Aoki and Miyamoto do not subject their drug mixtures to temperatures greater than the melting temperature of the drug. The Examiner admits that Aoki does not teach that the temperature

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[1] The Examiner refers to Miyamoto as describing HPMC-AS as an amorphous state-inducing agent on page 12 of the present Action. However, HPMC-AS is characterized by this reference as an amorphous state-*stabilizing* agent. See Miyamoto, Col. 5, line 65, through Col. 6, line 19.

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achieved during microwave irradiation is greater than the melting temperature of the drug in the mixture (Action dated May 12, 2009, page 10). Miyamoto emphasizes that its mixtures are heated to the amorphous-state induction temperature, which is lower than the melting temperature of the drug in the mixture. Miyamoto, Col. 3, lines 23-56 (use of an amorphous state-inducing agent, such as succinic acid, depresses the melting point of the mixture of it with a medical substance); Col. 4, lines 31-43 (it is preferable to depress the melting point of the mixture to 5°C, 15°C, or 25°C or more as compared to the melting point of the medicament); Col. 7, lines 16-19 (heating is applied at the amorphous state-induction temperature). Thus, in failing to teach microwave irradiation modulation, the cited art not only fails to teach using such modulation to reach a temperature of the mixture that is greater than the melting temperature of the drug, but also fails to teach maintenance of that temperature for at least 5 minutes. Nothing in the Examiner's "Response to Arguments" in the present Action points to a teaching or suggestion of these claimed elements.

The significance of modulation versus constant power is exemplified in reference Examples 5 and 6 of the present specification. In each of these Examples, microwave irradiation of constant power was applied to a drug/carrier mixture. As a result, only low conversion of the drug into amorphous form was achieved (Example 5), or the mixture was carbonized (Example 6). Applicants note Example 6 in particular, as a drug was employed in combination with cross-linked polyvinylpyrrolidone, which is an amorphous-state stabilizing agent according to Miyamoto (Col. 5, lines 18-26). When this mixture was subjected to constant microwave irradiation, the mixture completely decomposed.

Applicants also note a comparative experiment that was conducted but not included in the specification as originally filed. This experiment was described by the applicant in proceedings before the European Patent Office regarding the related PCT and EP applications (see

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Appendices 1 and 2). In this experiment, a mixture of ibuprofen and β-cyclodextrin was wetted with water and subjected to microwave irradiation of constant power. Miyamoto explains that β-cyclodextrin is an amorphous state-stabilizing agent (Col. 5, lines 18-46). After only 5 minutes, the mixture decomposed, leaving only a carbonized residue. By contrast, when a mixture of ibuprofen and β-cyclodextrin was wetted and subjected to modulated microwave irradiation to a temperature (90°C) that is above the melting temperature of ibuprofen (75.6°C) and maintained for at least 5 minutes at this temperature, a composite having the desired drug dispersal was obtained. Specification, Example 1.

The foregoing comparative examples demonstrate that microwave irradiation modulation as recited in the claims successfully permits a mixture to be heated to temperatures above the melting temperature of the drug in the mixture such that a composite having the desired drug dispersal results. Neither Aoki, Miyamoto, nor a combination thereof teaches or suggests this aspect of the claims. As such, there is no "apparent reason" to rely on either or both of these references in an obviousness rejection. See *KSR Int'l Co. v. Teleflex*, 127 S. Ct. 1727, 1741 (2007) (there should be an explicit analysis regarding "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). Withdrawal of the rejection is requested for at least this reason.

B. "the melting point of the drug" and "the drug"

Applicants wish to address the Examiner's first point in the "Response to Arguments" section of the Action. Here, the Examiner asserts the following:

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> In response to Applicants' arguments that the references fail to show certain features of Applicants' invention, it is noted that the features upon which applicant relies (i.e., "the melting point of the drug" and "the drug") are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Action, page 11. Applicants respectfully question what the Examiner is referring to. Applicants do note that on page 16 of the October 2009 response, last paragraph, applicants did recite, "Nowhere does Miyamoto suggest that this translates to heating a mixture to a temperature that is greater than that of the melting point of the drug in the mixture, much less maintenance of that temperature for at least 5 minutes." (Emphasis in original). Applicants submit that use of the term "melting point" instead of "melting temperature" in this sentence is a distinction without a difference. Indeed, applicants note that the Examiner interchanges "melting point temperature" and "melting point" on page 12 of the Action. Applicants believe it is clear that "melting point of the drug" recited in this sentence was intended to be equivalent to "melting temperature of the drug," as recited in the claims. As such, applicants respectfully reiterate the arguments set forth at pages 14-19 of the October 2009 response that contrast the melting temperature as recited in the claims with the melting temperatures discussed in the art.

III. Claims 4, 5, 9, and 21 Are Patentable Over Miyamoto

Claims 4, 5, 9, and 21, which depend from Claim 1, are rejected as obvious over Miyamoto. Applicants respectfully disagree. As discussed above with respect to Claim 1, this reference fails to teach every element of the claimed invention; as such, there is no "apparent reason" why a skilled artisan would look to this reference to arrive at subject matter of the rejected claims. See *KSR*, 127 S. Ct. at 1741. Thus, as with Claim 1, these dependent claims are also not obvious over the art. Applicants therefore respectfully request withdrawal of the rejection.

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IV. Claims 6 and 7 Are Patentable Over Miyamoto, Aoki, and Lautenschläger

Claims 6 and 7, which depend from Claim 1, are rejected as obvious over Miyamoto, Aoki, and Lautenschläger (U.S. Patent No. 5,447,077). Applicants respectfully disagree. As discussed above, Miyamoto and Aoki, either separately or together, fail to teach or suggest every element of the claimed invention. Lautenschläger fails to account for this deficiency, as this reference is directed towards devices for evaporation treatment of a sample material in a container. Lautenschläger, Abstract. As such, there is no "apparent reason" why a skilled artisan would combine these references in an attempt to arrive at subject matter of the rejected claims. See *KSR*, 127 S. Ct. at 1741. Because these dependent claims are not obvious over the art, applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing remarks, applicants believe that Claims 1-10 and 21 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1649.

Respectfully submitted,

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APPENDIX 1

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EUROPEAN PATENT OFFICE
Attn. Officer RAUTER A
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GERMANY

Milan, 15 February 2005

Re.: International Patent Application No. PCT/EP03/14740 filed on 22.12.2003
In the name of EURAND S.P.A. et al.
"Stabilised Solid Drug dispersions In An Organic Carrier And A Process..."
Our Ref.: 2509PTEP/MAU/la

Dear Sirs,

We are writing with reference to the written opinion issued for the above identified patent application and in response thereto We submit herewith a comparative Example and a new set of amended claims to replace the one currently on file.

In the new claims submitted herewith the following amendments have been carried out:

- A new claim 1 has been introduced, directed to the process of the invention, wherein the specific conditions under which treatment with microwaves is carried out have been clearly specified. Support for the new claim can be found in the description at page 6, lines 1-5 and in the passages going from page 7, line 9 to page 8, line 9.

- New claims 2 and 3 have been introduced. Support for these claims can be found in the description at page 6, lines 13-15.

- Claim 4 to 7 correspond to former claims 13, 14, 16 and 17, respectively.

- Claim 8 correspond to former claims 15 and 18.

- Claim 9 relates to the process of the invention wherein specific cross-linked polymers are used. This claim finds support in former claim 4.

- Claim 10 refers to the process of the invention wherein specific drugs are used. This claim finds support in former claim 8.

- Claim 11 corresponds to former claim 1, which has been amended in order to exclude from its scope composites wherein the organic carrier is a cross linked polymer.

- Claims 12 to 20 correspond to former claims 5, 2, 3, 6-11, respectively.

- Former claims 12 and 19 have been deleted.

1. NOVELTY:

In the Written Opinion the Examiner asserts that the subject matter of claim 1 is already disclosed in Documents D1 to D5 and therefore claims 1-11 and 19 are not new in view of this prior art.

The Examiner will note that, in order to overcome this objection, the Applicant has amended former claim 1, now claim 11, to exclude from its scope composites wherein the organic carrier is a cross-linked polymer. Therefore, claim 11 is now directed exclusively to composites containing an organic carrier chosen from cyclodextrins and maltodextrins.

Documents D1, D3, D4 and D5 all disclose solid dispersions of a drug in polymeric matrixes.

In fact:

Document D1 discloses amorphous solid dispersion compositions containing a sparingly water-soluble drug blended with a **water-soluble polymer** and, optionally salicic acid.

Document D3 discloses substantially amorphous solid solutions containing a slightly water soluble antifungal compound dispersed in a matrix of a **soluble polymer**, preferably povidone or of an insoluble polymer, preferably crospovidone.

Document D4 discloses solid solutions and processes for their preparation that substantially correspond to those of D3.

Document D5 discloses a process of amorphisation of a sparingly soluble drug, such as nifedipine and indomethacin, by co-grinding of the drug with **"bridged" polyvinylpyrrolidone.**

Therefore, none of the above documents anticipate in any way the composite of new claim 1.

As regards document D2, this patent discloses a solid dispersion obtained by high frequency heating of a mixture of a drug and an amorphous state-stabilising agent. α-, β-, and γ-cyclodextrins are generically mentioned among a list of other 17 compounds as examples of amorphous state-stabilising agents. However, no specific disclosure of solid dispersions containing cyclodextrins or similar compounds or of specific conditions to be used for their preparations is provided in the document.

In fact, in the Experimental section of D2 it is only described the preparation of amorphous solid dispersions of drugs in hydroxypropylmethylcellulose-acetate succinate (Ex. 4, 5 and 6) or polyvinyl pyrrolidone. (Ex.7). These are water soluble polymers in no way related or equivalent to cyclodextrin. In all the Examples the preparation of the solid dispersion using these polymers is carried out irradiating the drug-polymer mixture with microwaves under conditions of constant power (700 W).

As will be explained in details when discussing on inventiveness of the process of the present application, the conditions of microwave treatment used in the Experimental section of D2 with hydroxypropylmethylcellulose-acetate succinate or polyvinyl pyrrolidone are not suitable to produce solid dispersions in cyclodextrin or cross-linked polyvinilpirrolidone. In fact, as demonstrated by the comparative Example submitted herewith and Example 6 of the patent application when these conditions are used with these specific carriers, degradation of the sample is observed.

Thus, the teaching contained in document D2, lacking to provide the means to obtain them, does not render accessible in any way solid dispersions containing cyclodextrins.

On the contrary, in the present application the inventors have disclosed specific conditions under which amorphous solid dispersions of a drug in cyclodextrins, maltodextrins or cross-linked polyvinylpirrolidone can be obtained by microwave treatment.

In view of the above discussed arguments and amendments, the Applicant submits that novelty should be recognised for new claims 11 to 20.

2. INVENTIVE STEP

In the Written Opinion the Examiner has also objected that former claims 12 to 18 lack inventive step in view of Documents D1 and D2.

D1 discloses a process for obtaining a solid dispersion compositions wherein a mixture of a sparingly water-soluble drug, a **water soluble polymer** and, optionally, salicic acid are exposed to microwaves. In all the Examples tablets containing nifedipine, macrogol 6000 and salicic acid anhydride are prepared and then exposed to microwaves operating at a **constant power** of 630W.

D2 discloses a process wherein a mixture of a drug and an amorphous state-stabilising agent is subjected to high frequency heating up to a **temperature** that it is **lower than the melting point** of the drug. The high frequency heating is carried out at a **constant power** (see in particular Examples 4 to 7). A long list of polymeric and non-polymeric compounds suitable to be used as amorphous state-stabilising agents is given (see col. 5, lines 18-60). Among these also cyclodextrins and cross-linked polyvinyl pyrrolidone are listed. However, all the Examples are carried out using HPMC or polyvinilpirrolidone, that are water soluble polymers.

According to the Examiner, the process of former claim 12 differs from that of Document D1 only in that a specific duration of the microwave treatment has been specified. Thus, since there are not time limits for the microwave treatment in D1 there would be no reason why the skilled man should not try to irradiate for a time as that indicated in former claim 12. Furthermore, the Examiner is of the opinion that also Document D2 be very pertinent to the process claims of the present invention.

The Applicant respectfully submits that the operating conditions under which the process claimed in new claim 1 is carried out are very different from those of the processes of D1 and D2 and could in no way be derived by the teaching contained in these documents.

Firstly, as it has now been clearly highlighted in new claim 1, an essential feature of the process of the present invention is that the microwave treatment must be carried out **modulating the microwave power**, thus varying it during the irradiation process, so that the mixture active principle-organic carrier is heated up to a temperature higher that that of the melting temperature of the active principle and it is then maintained **steady** at that **temperature** for at least five minutes.

This feature is not disclosed or suggested in neither D1 or D2. On the contrary, these two documents both teach that the treatment with microwaves must be carried out keeping the **power constant**. This results in a very different effect on the temperature of the sample compared to that observed with the microwave treatment of claim 1. In fact, as it is discussed in the description of the present application (from page 7, line 9 to page 8, line 22), when the microwave power is maintained constant the **temperature** of the sample does not remain steady but **increases** gradually.

Thus, firstly, there would be no reason why the skilled man, starting from the teachings of D1 and D2, would be induced to use the operative conditions of the process of claim 1, that lead to a completely different heating profile of the drug-carrier mixture and therefore to unexpected results.

Furthermore, the present inventors have found that when the microwave treatment is carried out under constant power, as taught in Document D1 and D2, it is not possible to obtain an amorphous dispersion of the active principle in the specific organic carriers claimed in claim 1, that are different from those used in the processes of Document D1 and D2.

In fact, as it is demonstrated in Example 6 of the patent application and in the Comparative Example submitted herewith, when a mixture of a drug with a cross-linked polymer or a cyclodextrin is treated under conditions of constant power, degradation of the sample is obtained within five minutes.

Regarding the process of Document D2, the Applicant would also like to highlight that the process disclosed therein also differs from the process of the present invention in that it requires that the temperature of the mixture is kept under the melting temperature of the drug. This teaching leads the skilled man further away from the process as claimed in present claim 1, wherein the drug must be melted during the microwave treatment.

Therefore, the Applicant respectfully submits that an inventive step should be recognised for claims 1 to 22 over the prior art cited by the Examiner.

In view of the arguments and amendments filed herewith, the Examiner's favourable reconsideration is respectfully requested.

Respectfully submitted

The Representative

Gemma Gervasi

NOTARBARTOLO & GERVASI

Enc.: Amended Set of Claims 1-20
Comparative Example

AMENDED CLAIMS

1) A process for the preparation of a composite containing a drug dispersed in an organic carrier, wherein the drug is massively dispersed (in bulk) within the particles of said organic carrier and it is present in amorphous form in a quantity greater than or equal to 50%, comprising the following steps:
a) forming a mixture of a drug with an organic carrier selected from the group consisting of water-soluble complexing agents chosen from cyclodextrins and maltodextrins, water-insoluble cross-linked polymers and mixtures thereof;
b) irradiating the mixture obtained in a), with microwaves, wherein the microwave power is modulated so that the temperature of the mixture increases until it reaches a value higher than the melting temperature of the drug and it is then maintained constant at said value for at least 5 minutes.

2) Process according to claim 1, wherein in step a) a wet mixture is formed by adding a solvent.

3) Process according to claim 2, wherein said solvent is water.

4) The process according to claim 3, in which said wet mixture is formed by adding water to the carrier-drug composite in a quantity comprised of between 0.1 ml/g and 5 ml/g with respect to the dry mixture of the composite.

5) The process according to claims 2 to 4, in which the pressure at which the irradiation is carried out is comprised of between 1 and 20 bar.

6) A process according to claims 1 to 4, wherein step b) is carried out in a container constituted of a dielectric material having coupling capacity with the microwaves.

7) The process according to claim 6, wherein said dielectric material is polytetrafluoroethylene loaded with graphite.

Comparative Example

An homogeneous mixture of 1 g of Ibuprofen and 9 g of β-cyclodextrin was wetted with 2 g of water. The wetted mixture thus obtained was placed into a teflon reactor and treated with microwaves (2.45GHz) with a power of 700 W. After less than 5 minutes the mixture was completely decomposed leaving only a carbonised residue.

APPENDIX 2

NOTARBARTOLO & GERVASI

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Milan, 19th December 2008

Re.: European Patent Application No. 03813592.7-1219
In the name of EURAND S.p.A.
Our Ref.: 2509PTEP/CAT/La

Dear Sirs,

With reference to the Communication pursuant to Art. 94(3)EPC dated August 14, 2008, the following documents are filed:

Original Page 2, after line 29; insertion of [A]

[A]: discussion of the relevant prior art documents D3-D5 as requested by the Examiner. Please note that the discussion of relevant prior art documents D1 and D2 is already present on page 2, lines 23-29.

Fresh Pages 2 and 2A with [A] inserted for clarity purposes

Original Page 3, line 2: correction of "degre" in "degree"

line 28: correction of "crosspovidone" in "crospovidone"

line 30: correction of "crosspovidone" in "crospovidone"

Original Page 4, line 1: correction of "crosspovidone" in "crospovidone"

Original Page 5, line 5: correction of "crosspovidone" in "crospovidone"

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Original Page 7, line 16: deletion of "as non-limitative indication" and addition of "for example"

Original Page 9 last line: deletion of "which do not have limiting function" and insertion of "for illustrative purposes"

Original Page 10: line 16: correction of "crosspovidone" in "crospovidone"

Original Page 12, lines 4, 11, 12: correction of "crosspovidone" in "crospovidone"

Original Page 13, line 5: correction of "crosspovidone" in "crospovidone"

Original Page 14, lines 2, 14: correction of "crosspovidone" in "crospovidone"

Original Page 17, lines 2,4,15,16: correction of "crosspovidone" in "crospovidone"

Original Page 18, lines 5,19: correction of "crosspovidone" in "crospovidone"

Original Page 19, line 2: correction of "crosspovidone" in "crospovidone"

Pages 21-23: a fresh set of claims 1-19

BASIS FOR AMENDEMENTS (reference to claims 1-20 filed on September 29, 2007):

Fresh claim 1 corresponds to previous claim 1 filed on September 29, 2007 amended with inserting: - the two conditions of the process as requested by the Examiner in order to overcome the objection under Art.123(2) EPC (Support for the amendment can be found on page 3, lines 9-13); - the statement "with respect to the total of the drug present" as agreed with the Examiner during the telephone conversation of August 1, 2008.

Fresh claims 2-5 are the previous claims 2-5;

Previous claim 6 has been deleted because of its insertion in Claim 1;

Fresh claim 6 is the previous claim 7 wherein the dependence has been amended;

Fresh claims 7-9 are the previous claims 8-10 wherein the dependence has been amended;

Fresh Claim 10 is the previous claim 11 filed on September 29, 2007, amended by re-inserting the features as in Claim 11 of entry into the regional phase;

Fresh claims 11-19 are the previous claims 12-20 wherein the dependence has been amended.

ARGUMENTS IN SUPPORT TO PATENTABILITY:

NOVELTY (Art. 54(2) EPC)

The Examiner objected the previous Claim 11 because it was defined as a product-by-process Claim.

The fresh Claim 10, not only defines the product with the available composition features, but also by specifying that it is a product-by-process, because the processes according the present invention affect the characteristics of the final product, being therefore a true feature characterizing the product. No other way of describing the effects of the process on the product can be used, being this definition in accordance to the EPC.

Specifically, the present process contains as essential feature that the microwave treatment must be carried out modulating the microwave power, thus varying it during the irradiation process so that the mixture active principle-carrier is heated up to a temperature higher than the melting temperature of the active principle and then it is maintained steady at such a temperature for at least five minutes. This heating cycle carried on the drug-carrier mixture affects the amorphous dispersion of the active principle (being at least of 50%) and contemporaneously maintained the drug in a not-degradated state.

This is confirmed by the present application on page 7, line 9, wherein it is stated that "*The microwave cycle is fundamental according to the present invention*" and on page 10, lines 10-22 "*In this respect it is important to remark that a melting substance absorbs energy in irregular way, depending on the relative amount of phases (solid, liquid), it goes during heating.....Such compensations are obtainable by available means of electric systems capable to detect any changes in the sample temperature and to modify immediately....*" Therefore, the treatment with microwaves affects the sample during the preparation and evidently the final characteristics. This will be more clear below by comparing the present product with the product as obtained by D2.

D2 describes a solid dispersion obtained by high frequency heating of a mixture of a drug and an amorphous state-stabilizing agent. Among a list of amorphous state-stabilizing agents, alpha, beta and gamma-cyclodextrins are cited. No specific disclosure of solid dispersions containing a drug and a cyclodextrin or a maltodextrin is provided in the document. In the experimental part of the document, examples 4, 5 and 6 relate to drug dispersions in hydroxy-propylmethylcellulose and example 7 relate to a drug dispersion in polyvinylpirrolidone. In all the examples the preparation of the solid dispersion using these polymers is carried out by irradiating the drug-polymer mixture with microwaves under the conditions of constant power (700 W).

The fresh claim 10 relates to a composite containing a drug dispersed **in carrier consisting of a water soluble complexing agent selected from cyclodextrins and maltodextrins**, wherein the drug is massively dispersed (in-bulk) within the particles of said complexing agent and it is present in amorphous form in a quantity greater than or equal to 50 % by weight, with respect to

the total of drug present in the composite and obtainable by a process, **wherein the microwave power is modulated in step b) of irradiation.**

First of all, the Applicant traverses the reasoning of the Examiner affirming that the novelty of the previously presented claim 11 can not be recognized also in view of the fact that the list of amorphous state-stabilizing agents in D2 (from the last paragraph of column 5 to the first paragraph of column 6) is a short list and not a "relatively long list" as stated by the Board of appeal decision. According to the Applicant such a list can be deemed a "relatively long list" for selecting the specific cyclodextrin, in view, also, of the fact that the examples of D2 refers only to cross-linked polymers and not "complexing agents" as maltodextrin and cyclodextrin as stated in the fresh claim 10.

The Examiner also asserts that in the final dispersion of example 4 of D2 the drug should be completely amorphous. Even if the drug in the dispersion of example 4 is not crystalline, however, such example does not exclude that the drug can be degradated under a constant power of 700 W. As a matter of fact, the way of carrying out the irradiation critically affects the final product as explained above.

As stated in the present application in the comparing example 6, nifedipine and an amorphous state-stabilizing agent, as a wetted mixture, were subjected to constant power as in example 4 of D2. Specifically, in a teflon reactor the wetted drug-mixture was treated with microwaves (2.45GHz) with a power of 700 W for 20 minutes. However, after only 5 minutes of treatment the mixture was completely decomposed leaving only a carbonised residue.

The Applicant carried out a second comparative Example submitted during the International Examination phase for the purpose of the IPER. The example was as follows:

"*An homogeneous mixture of 1 g of Ibuprofen and 9 g of β-cyclodextrin was wetted with 2 g of water. The wetted mixture thus obtained was placed into teflon reactor and treated with microwaves (2.45GHz) with a power of 700 W. After less than 5 minutes the mixture was completely decomposed leaving only a carbonised residue.*"

Therefore, in the specific condition of the fresh Claim 10, therefore with β-cyclodextrin, by applying a constant power of 700 W as in example 4, the drug degradated.

These two tests confirm that the specific process features of claim 10 really affect the final product, conveying it in a specific condition.

In view of the above, the fresh claim 10 is new over D2.

D3 and D4, which almost completely corresponds to D3, disclose substantially amorphous solid solutions of an antifungal agent and a soluble or insoluble polymer. Such documents are not relevant for novelty because they do not relate to a composite containing a drug dispersed in carrier consisting of a water soluble complexing agent selected from cyclodextrins and maltodextrins. As a

matter of fact D3 and D4 describe solid solutions comprising cross-linked polymers, as crospovidone or croscarmellose. In the fresh claim 10 the carrier is a complexing agent and not a cross-linked polymer. Furthermore, when D3 or D4 refer to "substantially amorphous" they apply this term to the solid solutions and not to the drug as in present Claim 10. Therefore, Claim 10 is novel over D3 or D4, singularly considered in the evaluation.

Inventive Step (Art.56EPC).

D2 is deemed to be the closest prior art for evaluating the inventive step of present Claim 10.

In view of D2, the objective problem is providing a composite of sparingly soluble drug having high solubilisation kinetics, which can be used directly as pharmaceutical composition.

This problem has not been solved by D2, because it teaches to prepare solid dispersions of a drug in a cross-linker polymer by subjecting it to a continued power thus not avoiding the risk to carbonize the drug in the matrix.

This problem has been solved by the fresh Claim 10, which relates to a composite of a drug dispersed in carrier consisting of a water soluble complexing agent selected from cyclodextrins and maltodextrins, which is obtainable by the present process, that guarantees to obtain a composite with a not-degradated drug by subjecting the mixture of the drug and the complexing agent to a specific heating cycle, thus allowing the not-degradated drug to be massively dispersed (in-bulk) within the particles of said complexing agent and to be present in amorphous form in a quantity greater than or equal to 50 % by weight.

In view of the foregoing, the Applicant hence respectfully requests for a favourable reconsideration of the present set of Claims. Should the Examiner unexpectedly decide to reject the application, the Applicant requests oral proceeding pursuant to Art. 116 EPC.

Respectfully submitted
The Representative

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Enc.: as above